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COCCIDIAL COMPOSITIONS CONTAINING LOWER ALKYL ESTERS OF 6,7-DI(LOWER) ALKOXY - 4 - HYDROXY - 3 - QUINOLINE-CARBOXYLIC ACID

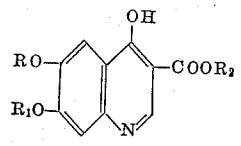
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1 Claim. (Cl. 167—53.1)

This application is a division of my copending application Ser. No. 272,858, filed Apr. 15, 1963, and now abandoned and a continuation-in-part of my copending application Ser. No. 242,933, filed Dec. 7, 1962, which, in turn is a continuation-in-part of my application Ser. No. 185,806, filed Apr. 9, 1962, now abandoned; and is filed as a substitute therefor.

This invention relates to new chemical compounds, lower alkyl esters of 6,7-di (lower) alkoxy-4-hydroxy-3-quinolinecarboxylic acid, represented by the formula:



wherein R and R_1 each represent a member of the group consisting of a lower alkyl radical containing from two to four carbon atoms and R_2 represents a lower alkyl group.

These new compounds are distinguished by the high order of chemotherapeutic activity which they exhibit in the treatment of parasitic infections in animals when administered in far less than toxic amounts. They have proved surprisingly successful upon oral administration in combatting coccidiosis.

Coccidiosis, a prevalent and economically significant disease of poultry, is caused by a variety of coccidia including *Eimeria tenella, Eimeria acervulina* and *Eimeria necatrix*. The new compounds of this invention are highly effective agents against such coccidia. When incorporated in a nutritionally balanced diet at a level of from about 0.006 to about 0.1% by weight and offered to coccidially infected chickens, they overcome the mortality and morbidity usually associated with coccidial disease and accomplish a salutary effect upon growth and appearance of the birds.

The preparation of these new compounds in a form permitting convenient administration is readily accomplished by admixing them in the diet of animals as indicated hereinabove. They may, if desired, be incorporated in tablets, gelatin capsules, suspensions or like compositions consisting of suitable carriers and adjuvants common to the pharmaceutical art.

The method which is currently preferred for the preparation of the new compounds of this invention consists in reducing a 1,2-dialkoxy-4-nitrobenzene in the presence of a catalyst such as palladium-on-carbon and a solvent such as ethanol; addition of the appropriate dialkylalkoxymethylene malonic ester; for instance, diethylethoxymethylene or dimethylmethoxymethylene malonate, to

the solution of the reduced product; removal of the solvent; and addition of a temperature regulating medium such as Dowtherm ® followed by application of heat to the mixture.

Other lower alkyl esters may be prepared by the saponification of one of them followed by subjecting the acid formed to the Fisher-Speier or Schotten-Baumann reaction. Still another method for preparing various lower alkyl esters consists in the transesterification technique whereby one alcohol moiety is exchanged for another.

In order that this invention may be fully available to and understood by those skilled in the art, the following examples for preparing the compounds thereof are described briefly:

Example I.—Ethyl 6,7-diethoxy-4-hydroxy-3-quinolinecarboxylate

1,2-diethoxy-4-nitrobenzene (30 g., 0.142 mole) is placed in a heavy-walled bottle with 3 g. of 5% Pd on carbon and 130 ml. of ethanol. In 1 hours, 38.5 p.s.i.g. of hydrogen is absorbed (theory 36.2). The catalyst is filtered off and washed with a small amount of ethanol.

In a 1 liter, 3-necked flask is placed the above alcoholic solution and 30 g. (0.142 mole) of diethylethoxymethylene malonate is added. Nitrogen is bubbled through the mixture, which is heated on the steam bath to distill off ethanol. After this, 300 ml. of "Dowtherm A" is added and the temperature rapidly raised to 250° C. by heating with a mantle. The mixture is allowed to reflux for 30–40 minutes and the solution is then allowed to cool. The crystals that form are filtered and washed with hexane. There are obtained 18.6 g. (61% yield); M.P. 275–280° C.; of ethyl 6,7-diethoxy-4-hydroxy-3-quinolinecarboxylate.

Calc. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.68; H, 6.25; N, 4.94.

Example II.—Ethyl 6,7-dibutoxy-4-hydroxy-3-quinolinecarboxylate

In a heavy-walled bottle is placed 29.48 g. (0.11 mole) of 1,2-dibutoxy-4-nitrobenzene, 200 ml. of ethanol and 3 g. of Pd on carbon. Theoretical uptake of hydrogen upon reduction of this mixture in a Parr apparatus is achieved in one hour (30 p.s.i.g.). The reduction is repeated with an equal amount of the nitro compound. The reduced material is combined, filtered and the catalyst washed with ethanol. The filtrate is placed in a 1 liter, 3-necked flask together with 47.5 g. of diethylethoxymethylene malonate. The mixture is heated on a steam bath and ethanol removed by distillation. "Dowtherm A" (600 ml.) is added and the mixture is rapidly heated to reflux (250° C.). After refluxing for 40 minutes, the mixture is cooled to room temperature. Hexane is added. The crystalline precipitate is filtered and washed with hexane. A 29% yield of crude ethyl 6,7-dibutoxy-4-hydroxy - 3 - quinolinecarboxylate is obtained (22.76 g.) (M.P. 260–285° C.).

This may be recrystallized from dimethylformamide using charcoal, if desired, to yield 19% of ethyl 6,7-dibutoxy-4-hydroxy-3-quinolinecarboxylate having a melting point of 279–284° C.

Calc. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.87. Found: C, 66.36; H, 7.42; N, 3.70.

Example III.—Ethyl 6,7-dipropoxy-4-hydroxy-3-quinolinecarboxylate

In a heavy-walled bottle is placed 38 g. (0.16 mole) of 2-dipropoxy-4-nitrobenzene, 200 ml. of ethanol and 3 g. of 5% Pd on carbon. The mixture is hydrogenated in Parr apparatus to give a hydrogen uptake of 41 p.s.i.g. theory 42 p.s.i.g.). This is repeated until a total of 72 g. (0.72 mole) of nitro compound has been reduced. The catalyst is filtered off and the ethanolic filtrates are combined for the next step.

The ethanolic solution is mixed with diethylethoxymethylene malonate (0.72 mole) and the alcohol is removed by distillation on a steam bath. Heating is continued for three hours. "Dowtherm A" (750 ml.) is added and the mixture is heated rapidly to reflux. The solution is refluxed for 30 minutes and allowed to cool. The crystalline precipitate is filtered and washed with hexane. The yield of title compound is 96 g. (40% yield from the nitro compound). It may be recrystallized from dimethylformamide (M.P. 271–273° C.).

Calc. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.70; H, 6.80; N, 4.43.

Example IV.—Methyl 6,7-diethoxy-4-hydroxyquinoline-3-carboxylate

A. In a 1 l. flask is placed the ester of Example I, 73 g. (0.24 mole), and 300 ml. of 10% sodium hydroxide solution. The mixture is refluxed for 2½ hours. Charcoal is added and the mixture is filtered hot. It is then allowed to cool. The mixture is acidified with about 200 ml. of 1:1 hydrochloric acid (100 ml. conc. hydrochloric acid and 100 ml. of water). A cream-colored precipitate forms. This is filtered, washed with water and allowed to dry overnight at 110° C. In this way, 6,7-diethoxy-4-hydroxyquinoline-3-carboxylic acid is obtained, M.P. 265–273° C. This may be recrystallized from dimethylformamide to give a melting point of 266–269° C. To 56 g. (0.2 mole) of the acid suspended in 1500 ml. of benzene is added 15 ml. (0.2 mole) of thionyl chloride with stirring. The mixture is heated at reflux with stirring for 8½ hours until no more HCl gas is evolved. After slight cooling, the solid is collected and washed well with benzene and then ether, yielding 56 g. (94.7%) of acid chloride, M.P. 260° C.

A suspension of 54.5 g. (0.185 mole) of the acid chloride in 1500 ml. of methanol is heated at reflux on the steam bath for 5½ hours. The reaction mixture is filtered hot and the filtrate cooled. The solid which separates is filtered and washed with ether; weight 13 g. On adding water to the original filtrate more solid is obtained which is collected and dried. A total of about 50 g. (93%) of crude product is obtained. Recrystallization from 3 l. of dimethylformamide and charcoal gives 35.0 g. of methyl 6,7-diethoxy-4-hydroxy - 3 - quinolinecarboxylate melting at 276.5–278.5° C.

Calc. for $C_{15}H_{17}NO_5$: C, 61.80; H, 5.83; N, 4.81. Found: C, 61.64; H, 5.93; N, 4.95.

B. 6.1 g. (0.02 mole) of the compound of Example I in 700 ml. of methanol and a small amount of p-toluene sulfonic acid is heated to reflux for 7 days. The reaction mixture is filtered hot and the solid is washed with ether and dried to give 2.3 g. of title compound, M.P. 275–278° C. By concentrating the original reaction mixture an additional 2.2 g. solid may be obtained. Total amount of title compound obtained is 4.5 g. (77.6%).

Example V.—Ethyl 6,7-diisopropoxy-4-hydroxy-3-quinolinecarboxylate

A. *o-Diisopropoxybenzene.*—A slow stream of nitrogen is passed through a solution of 220 g. (2 moles) of catechol in 900 ml. of alcohol in a 3 l. 3-necked flask equipped with stirrer, reflux condenser, dropping funnel and nitrogen inlet. After a few minutes stirring, 160 g. (4 moles) of sodium hydroxide is added and stirring is continued until practically all of the sodium hydroxide has dissolved. To the stirred, thick suspension is added 750 g. (6 moles) of 2-bromopropane over a 2-hr. period, maintaining gentle refluxing by means of a steam bath. After the addition, the nitrogen is turned off and refluxing is continued for 18 hrs. The mixture is cooled thoroughly and the sodium bromide is filtered and washed with alcohol. The combined filtrate and washings are concentrated in vacuo until as much alcohol as possible has been removed. A further amount of sodium bromide which separates during the concentration is removed; a total of 390 g. of sodium bromide (95% of calcd.) was obtained.

The oily residue is dissolved in 500 ml. of ether and extracted with four 200 ml. portions of 10% sodium hydroxide solution, then with two 100 ml. portions of water.

The ether solution is dried over magnesium sulfate and concentrated, first at atmospheric pressure and then in vacuo, to an amber-colored oil weighing 182 g. (47% of theory for diisopropoxybenzene).

B. *1,2-diisopropxy-4-nitrobenzene.* — o-Diisopropoxybenzene (140 g., 0.72 mole) is added dropwise to a stirred solution of 90 ml. of concentrated nitric acid in 90 ml. of water over a period of one hour. The temperature is maintained at 20–25° C. by intermittent application of an ice-bath. Stirring is continued until all exothermic reaction has ceased. The reaction mixture is diluted with an equal volume of ice-water and the dark, oily product is extracted with three 250 ml. portions of chloroform. The combined chloroform extracts are washed with three 100 ml. portions of water and dried over magnesium sulfate. An equal volume of carbon tetrachloride is added and this solution is poured onto a 60 x 600 mm. column of alumina (Merck 71707; ca. 3.5 lbs.). The column is eluted with a mixture of equal parts of chloroform and carbon tetrachloride at a flow rate of 30 ml./min. After collection of ca. 3 l. of yellow solution, the eluate became almost colorless, a dark brown zone remaining at the top. Concentration of the yellow eluate in vacuo gives 100 g. (58%) of the titled nitro compound as a yellow oil.

C. *Ethyl 6,7-diisopropoxy - 4 - hydroxy-3-quinolinecarboxylate.*—A 20 g. portion (0.084 mole) of 1,2-diisopropoxy-4-nitrobenzene is hydrogenated over 2 g. of 10% palladium-charcoal catalyst in 200 ml. of alcohol at 40 p.s.i. initial pressure. The reduction ceases after a pressure drop of 23 lbs. (87% of calcd.) in 30 min. The catalyst is filtered, 18 g. (0.084 mole) of diethylethoxymethylenemalonate is added and the solution is heated under reflux for 2 hrs. The amber-colored, oily residue remaining after distillation of the alcohol in vacuo is added to 900 ml. of "Dowtherm A" at ca. 245° C. This solution is boiled for 30 min., then allowed to cool overnight. The crude product is filtered, washed with "Dowtherm," then with benzene and dried at 80° C.; 9.7 g. (35%) of the title compound is obtained as light tan crystals, M.P. 220–228° C. Recrystallization from dimethylformamide gives 6.4 g. of white crystals, M.P. 233–234° C.

Calc. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.53; H, 6.94; N, 4.37.

Example VI.—Methyl 6,7-diisopropoxy-4-hydroxy-3-quinolinecarboxylate

A 25 g. sample (0.11 mole) of 1,2-diisopropoxy-4-nitrobenzene (Example V, B.) is hydrogenated over 4 g. of 5% palladium-charcoal catalyst containing 50% water in 200 ml. of alcohol at 40 p.s.i. initial pressure. The reaction ceases after a pressure drop of 23 lbs. (87% of calcd.) in 30 min. The catalyst is filtered and to the combined filtrates from two such reductions is added 38 g. (0.22 mole) of dimethylmethoxymethylenemalonate in 200 ml. of alcohol. This solution is heated under reflux for 1¼ hrs. and then concentrated in vacuo to a viscous residue.

This residue is heated on a steam bath and added to

1400 ml. of "Dowtherm A" preheated to 245° C. The solution is boiled for 20 minutes; then allowed to cool. The crude product is filtered, washed with "Dowtherm," then with acetone and air-dried; 25 g. (40%) of the title compound is obtained, M.P. 244–252° C.

Recrystallization of 52 g. of this product from 550 ml. of dimethylformamide gives 43 g. of white crystals, M.P. 253–256° C.

Calc. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 64.03; H, 6.52; N, 4.53.

What is claimed is:

A composition having anticoccidial properties and suitable for administration to animals, comprising 0.006 to about 0.1% by weight of at least one lower alkyl ester of 6,7-di(lower)alkoxy-4-hydroxy-3-quinolinecarboxylic acid in which the ether groups contain from two to four carbon atoms in admixture with an edible carrier.

No references cited.

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